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(O vozmozhnosti opredeleniya predel'nykh doz kantserogennykh veshchestv)

I. N. Neyman

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THE POSSIBILITY OF DETERMINING MAXIMUM DOSES OF CARCINOGENIC SUBSTANCES

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The question of determining doses of carcinogenic substances which are safe for man has great theoretical and practical value. Our environment contains not a few carcinogenic active chemical mixtures of the most varied origins, and it is natural that hygienists, toxicologists and oncologists are interested in the possibility of establishing maximum permissible concentrations of such substances in the atmosphere, soil, drinking water, food products, etc.

For a valid approach to this problem, it is first of all necessary to ascertain the following. Does the literature contain conclusive data indicating the safety of very small doses of chemical carcinogenic substances? If carcinogenic substances, administered in very small doses, do not actually cause the development of a tumor, then do they not create in the organism subjected to their influence heightened sensitivity to the effect of carcinogenic factors? Can answers to these questions regarding any group of carcinogens be attributed to all kinds of chemical carcinogenic substances, i.e. is the mechanism of the effect of carcinogens and the course of development of a precancerous condition and a malignant tumor under their influence of importance here?

We shall attempt to answer.

In studying the effect of various doses of carcinogenic polycyclic aromatic hydrocarbons (PAH), it was found conclusively that the smaller the dose of carcinogen, the fewer tumors developed in test animals and the longer the time required for the neoplasm to develop (Dobrovolskaia-Zavadskaia; Shear and Lorenz; Oberling et al.; Bryan and Shimkin; Poel and Kammer; Poel; Arthur and Eastlick, and others). However, a limit could not be established, as in a small number of animals and over a long period of time tumors, nevertheless, do

appear, even from micrograms of the carcinogenic substance or even fractions thereof.

Data from our laboratory (I. N. Neyman and A. Ya. Sinay; M. M. Baygusheva), corroborated by other Soviet (Ye. P. Koshnevnikova) and foreign (Saffiotti) researchers, showed that small doses of carcinogens (methylcholanthrene, benzpyrene, dibenzanthracene, orthoaminoazotoluene) do not actually cause tumors in test animals, but create in the organism heightened sensitivity to the effect not only of these, but also to carcinogens with a different mechanism of inducing tumors. If these animals were later subjected to the effect of ordinary doses of carcinogens, then tumors developed more quickly and from significantly smaller doses than in the control animals. It must be kept in mind that very small doses of carcinogens create in the organism such a pronounced tendency toward the development of the tumorous process that later the administration of noncarcinogenic or very weak carcinogenic substances is sufficient for tumors to develop rapidly and in a very high percentage (tests studying cocarcinogenesis; Shear; Berenblum, and others).

Does the above apply to the effect of all carcinogenic agents, regardless of the mechanism of their effect on the organism? It must be noted that conclusive data is available only about the carcinogenic activity of minimum doses of PAH; information concerning other carcinogens (amino compounds, aromatic amines, nitrous amines, etc.) is very limited and cannot presume complete reliability. Data on the activity of numerous weak carcinogenic chemical substances, when administered in extremely small doses, is evidently completely lacking.

Of basic importance here, undoubtedly, is the mechanism of the effect on tissues. Unfortunately, as yet there is no generally accepted division of chemical carcinogens by the mechanism of their effect if we are not speaking of the tropism of many to certain organs (azo-compounds such as orthoaminoazotoluene and para-amino-azobenzene to the liver, aromatic amines such as benzidine and betanaphthyl amine to the mucous membrane of the urinary bladder, urethan to lung tissue, etc.). However, the necessity of such classification is perfectly obvious. We attempted this in 1970. It seems to us that the possibility or impossibility of establishing maximum doses of carcinogenic sub-

stances should be considered from this standpoint as well.

It is generally accepted that cancer is a pathological process, developing against a background of a genetically-dependent tendency of human and animal tissues toward specific transformation of normal cells in one or another organ. Under the influence of exogenic or endogenic causes, ordinary, normal differentiation of cellular elements in the tissues is disturbed and instead of normal synthesis and reduplication of protein and nuclein systems, there occurs a peculiar shift to a new, pathological type of metabolism, the essence of which is the formation and accumulation of a material substratum specific for the malignant process -- pathological "cancerous" nucleoprotein systems. It is obvious that the appearance of malignant tumors in various conditions of spontaneous and experimental development follows different paths. Four types of such development can be cited.

1. A healthy organism receives a tumor virus, i.e. a specific material substratum for the tumorous process--an already-prepared "cancer" nucleoprotein complex. In the presence of a genetically-determined tendency of tissues in a given kind of animal and its individual susceptibility to the development of the malignant process, the introduced specific substratum enters into close contact with corresponding nucleoprotein systems and organizes a type of metabolism typical of the cancer process.

2. Tissue that is healthy but inclined toward the development of malignant processes receives an outside chemical carcinogen of the PAH type, i.e. having (as such or through its metabolites) a direct effect, organizing specific transformation of tissue elements. In accordance with the data presented above, even minimum doses of such a carcinogen causes so-called initiation of the malignant process in the tissues, specificity is created; the administration of a carcinogenic substance is not necessary for further development of the process. Specificity has already been created, further activation of the process can occur under the influence of even nonspecifically-acting substances, as is noted in cocarcinogenesis tests. Here, the carcinogen dose can be minimal and unaccompanied by subsequent contact of the organism with the carcinogenic agent. This state is characterized by weak nonspecific morphological precancerous changes in tissues, widely observed clinically in the development of spontaneous

tumors; these, evidently, do not play an essential role in the development of the process. It seems that safe doses of carcinogenic substances are impossible, as malignancy as a biological concept can develop from insignificant doses of a carcinogen; further development of the process can,in a clinical or morphological sense, only be accelerated by a new influence on tissue, even one with no carcinogenic activity.

3. Into healthy tissue inclined toward the spontaneous appearance of malignant tumors is introduced a substance with a necrotizing effect, however, not so strong that all the cells in a given section are killed. As a result, part of them die, and the rest begin to proliferate and create a posterity of cells with disturbed metabolism. The latter in turn are subjected to the effect of the necrotizing substance; then, cellular proliferation in such tissue continues under the combined influence of atrophic-degenerative and proliferative processes, which is the basic current concept of the precancerous condition.

In the presence of a corresponding predisposition in such tissue, a specific "cancer" set of pathological nucleoproteins can appear and often does. This is the material substratum for malignancy with subsequent morphological and clinical development of the malignant tumor. From this precancerous state, cancer can either develop or not. The decisive circumstance here is, evidently: does synthesis of a specific "cancerous" substratum develop with subsequent increased concentration or not? The precancerous process is nonspecific, and its conversion to cancer, i.e. the acquisition of specificity, is determined by the ability of underlying tissues, under corresponding conditions, to synthesize a specific material substratum. As an example, this is how spontaneously-developing malignant tumors arise. Clinical oncology long ago recognized as precancerous chronic inflammatory processes, proceeding with trophic disturbances, having a weak tendency to heal, with the prolonged coexistance of atrophic-degenerative and proliferative symptoms.

There are also chemical substances which, under experimental conditions, can, for example, by this method cause tumors to develop in animals. These substances have no direct oncogenic effect on tissues; they, evidently, are not organizers, in the strict sense of the word, of the malignant process, but only

create in tissues a precancerous condition, having a necrotizing effect and creating prolonged coexistance of atrophy, degeneration and proliferation. Characteristic of the effect of such substances is a morphologically pronounced pattern of precancer, which is not the case with the administration of "true" carcinogens, which have only a microtraumatic effect on tissues. Such substances, it seems to us, must be considered carcinogenic only conditionally. Such carcinogens must include CCl_4, which first causes necrosis in the liver, thiouracil preparations, which lead to the development of cancer in the thyroid gland against a background of long coexistance of degenerative and proliferative phenomena, plant derivatives such as aflatoxin which has a pronounced necrotizing effect on liver tissue.

All these substances are evidently not carcinogens in the strict sense of the word; they do not have the capacity for initiation. Their carcinogenic effect is based on the ability to cause rough damage to tissue and create in it a precancerous condition; therefore, a longer time is required for the development of cancer under their influence than with the administration of "true" carcinogens. Only these latter are direct organizers of the malignant process.

Therefore, the creation of a pronounced precancerous condition is necessary for the development of cancer under the influence of "conditional" carcinogens; of decisive importance, of course, is the degree of necrotizing effect of the substance in question, i.e. its dosage. Substances leading to the development of a pronounced precancerous condition, in our opinion, can and should be dosed, as they are dangerous in an oncological sense only in a certain stage of effect on tissues, unlike "true" carcinogens, for which dosage has no decisive meaning.

4. To complete the classification, we must mention a group of chemical substances which are not carcinogens as such, but under certain circumstances can lead to the development of cancer. Here are included glucose and other sugars, sodium chloride, estrogenic hormones, which when introduced into the organism in completely nonphysiological doses by seriously damaging exchange processes facilitate tumor development in the presence of a genetically-determined tendency toward it in the animal. Plastic and metal plates can lead to cancer by creating a mechanical barrier to normal metabolism, etc. Here we

must mention the development of tumors in the liver with nutritional imbalance, for example, with insufficient protein and choline in the diet.

Evidently, only "true" and "conditional" carcinogens (groups 2 and 3 in the above classification) must be included in considering the possibility of establishing permissible doses. It seems that no doses of the first can be called safe; the second can be standardized. However, we must not forget that during his lifetime, a person comes in contact with many carcinogenically-active factors, whose effect is usually cumulative. This forces us to regard with skepticism even the determination of acknowledged safe concentrations of these substances.

We must point out that the environment is polluted to a much greater degree with true carcinogens of the PAH type than all kinds of "conditional" substances. Permissible doses of chemical carcinogens must be determined, not in the food industry, from whose products they must be completely removed in view of the danger of cumulative effect, because of their entrance into the human organism from earliest childhood and through the entire lifetime, but primarily in the atmosphere, where pollution from factory, transportation and household waste makes it the source of large concentrations of "true" carcinogens--benzpyrine and other polycyclic aromatic hydrocarbons. Complete removal from the atmosphere at this time is naturally unrealistic. However, under the pretext of a lack of their maximum permissible concentrations in factory emissions, no attempts are being made to reduce pollution of the atmosphere by these products.

Remember, that although, in our opinion, harmless doses of carcinogenic PAH do not exist, nevertheless, the lower its dose, the fewer the tumors that develop from it and the longer the latent period of development. Sanitary inspection agencies in the shortest possible time should carry out those measures which will result in reducing the concentration of PAH in emissions and other waste in the environment. This can be realized with the continued cooperation of hygienists and technologists. Corresponding measures must also be conducted in motor vehicle and aviation transportation. Measures to control smoking in public places must not be forgotten, as the amount of PAH in tobacco smoke is considerable. At the same time, it is perfectly self-evident

that methodological disputes should not affect the implementation of sanitary measures to protect the environment from the emission of raw gases and aerosols.

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